Public Assessment Report
for paediatric studies submitted in accordance
with Article 45 of Regulation (EC) No1901/2006, as amended

Dexamethasone

MT/W/005/pdWS/001

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<tr>
<th>Rapporteur:</th>
<th>Malta</th>
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<tr>
<td>Finalisation procedure (day 120):</td>
<td>20/07/2012</td>
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<td>Date of finalisation of PAR</td>
<td>20/09/2012</td>
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**ADMINISTRATIVE INFORMATION**

| Invented name of the medicinal product(s): | Oradexon  
Aacidexam  
Dexamethasone  
Fortecortin |
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<tr>
<td>INN (or common name) of the active substance(s):</td>
<td>Dexamethasone</td>
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| MAH (s): | N.V. Organon, The Netherlands  
Organon Laboratories Limited, U.K  
Organon Portuguesa, Lda., Portugal  
Merck & Co., Inc. |
| **Comment:** | *At present N.V. Organon is an indirectly owned subsidiary of Merck & Co., Inc.*  
*Schering-Plough Central East AG located at Weyenstrasse 20, 6000 Lucerne 6, Switzerland, is an indirectly owned subsidiary of Merck & Co., Inc.*  
*The companies mentioned above, including their affiliates, are trading and operating under the trade name MSD outside the United States and Canada.* |
| Pharmaco-therapeutic group (ATC Code): | HO2AB02 |
| Pharmaceutical form(s) and strength(s): | 0,5mg, 1,5mg and 2mg tablets  
5mg/ml, 8mg/2ml, 4mg/ml Solution for Injection |
### ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>ACTH</td>
<td>Adrenocorticotropic hormone</td>
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<td>CRH</td>
<td>Corticotropin releasing hormone</td>
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<td>CTS</td>
<td>Corticosteroids</td>
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<tr>
<td>EC</td>
<td>European Community</td>
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<tr>
<td>HPA-axis</td>
<td>Hypothalamic pituitary adrenocortical axis</td>
</tr>
<tr>
<td>IM</td>
<td>Intramuscular</td>
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<tr>
<td>IV</td>
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<tr>
<td>MAH</td>
<td>Marketing Authorisation Holder</td>
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<tr>
<td>MEB</td>
<td>Medicines Evaluation Board, The Netherlands</td>
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<td>PdWS</td>
<td>Paediatric Work sharing</td>
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<tr>
<td>PL</td>
<td>Patient Leaflet</td>
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<tr>
<td>PSUR</td>
<td>Periodic Safety Update Report</td>
</tr>
<tr>
<td>RA</td>
<td>Rheumatoid arthritis</td>
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<tr>
<td>SmPC</td>
<td>Summary of Product Characteristic</td>
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I. EXECUTIVE SUMMARY

Since its introduction in 1959 dexamethasone has been effectively used in a wide variety of severe and/or serious conditions for which effective treatment had not been available before the introduction of corticosteroids (CTS). Dexamethasone is a powerful CTS which has the advantage over other steroids in that it has very little, if any, mineralocorticoid effects.

Data packages were submitted by the marketing authorisation holder (MAH) for paediatric work sharing (PdWS) for dexamethasone procedure, number MT/W/005/PdWS/001, in conformity with Article 45 of the Paediatric regulation (EC) 1901/2006 as amended.

Basing on published reports which appeared during the last two decades there are concerns about the long term risks of possible impaired neurodevelopment following the administration of high dose of dexamethasone to premature neonates in the first few days of life.

Changes are proposed in sections 4.4, 4.6 and 5.3 of the Summary of Product Characteristics (SmPC) and in the Patient Leaflet (PL).

Summary of outcome

☐ No change
☐ Change
☐ New study data: <section(s) xxxx, xxxx>
☑ New safety information: Section 4.4, 4.6 and 5.3
☐ Paediatric information clarified: Section 4.4
☐ New indication: <section(s) xxxx, xxxx>
II. RECOMMENDATION

In connection with Paediatric Work Sharing (PdWS) Procedure according to Article 45 of the Paediatric Regulation (EC) No. 1901/2006 as amended, basing on a review of the paediatric data submitted by the MAH regarding the treatment of children with dexamethasone, basing on consultation of the literature, basing on the comments of Member States and basing on the responses from the MAH following the Day 70 Preliminary Paediatric Assessment Report (PPdAR) it is recommended in the Final Assessment Report (FAR) for procedure number MT/W/005/PdWS/001 for dexamethasone, that in connection with the safety of children the following should be added to update sections 4.4, 4.6, and 5.3 of the currently approved Summary of Product Characteristics (SmPC) and to the Patient Leaflet (PL).

The recommendations for changes/additions to the SmPC and PL are as follows:

1. SmPC

Section 4.4 Special warnings and precautions for use:
Preterm neonates: “Available evidence suggests long-term neurodevelopmental adverse events after early treatment (< 96 hours) of premature infants with chronic lung disease at starting doses of 0.25mg/kg twice daily.”

Section 4.6 Pregnancy and lactation:
“Administration of corticosteroids to pregnant animals can cause abnormalities of foetal development including cleft palate, intrauterine growth retardation and effects on brain growth and development. There is no evidence that corticosteroids result in an increased incidence of congenital abnormalities, such as cleft palate/lip in man. See also section 5.3 of the SmPC.”

Section 5.3 Preclinical safety data:
“In animal studies, cleft palate was observed in rats, mice, hamsters, rabbits, dogs and primates; not in horses and sheep. In some cases these divergences were combined with defects of the central nervous system and of the heart. In primates, effects in the brain were seen after exposure. Moreover, intra-uterine growth can be delayed. All these effects were seen at high dosages.”

2. PL

The following information should be added under “Pay attention when using Dexamethasone”:

“Dexamethasone should not be used routinely in preterm neonates with respiratory problems.”

A Type IB variation to be requested from the MAH within 90 days of the publication of this Public Assessment Report (PAR).
III. INTRODUCTION

In connection with the PdWS procedure MT/W/005/pdWS/001 regarding dexamethasone the marketing authorisation holder (MAH) submitted the following documentation in accordance with Article 45 of the Regulation (EC) No. 1901/2006, as amended on medicinal products for paediatric use:

- Data, including published information, clinical and non-clinical relevant for the paediatric assessment

- A clinical expert overview clarifying the context of the data (Merck)

- A clinical expert overview on Oradexon (Schering-Plough Research Institute)

- Relevant periodic safety update report (PSUR) data

- A Report on Dexamethasone by the Netherlands Medicine Evaluation Board (MEB)

- SmPC proposals

Further references to the medical literature were included in the following sources:

1. From Merck: “Clinical Overview Addendum for Pediatric Use 2011”: 150 references

2. From Schering-Plough: “Clinical Overview on Oradexon” (October, 2009): 24 references

3. From the Medicine Evaluation Board (MEB) Report on dexamethasone (“The risks of administration of high dose dexamethasone to premature neonates”), The Netherlands (21 December 2008): 63 references

No paediatric study was submitted for this work sharing procedure.
IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the clinical study(ies)

The following is based on the data sent by the MAH regarding dexamethasone.

Oradexon (N.V. Organon) is a synthetic glucocorticoid preparation, with the proposed EU harmonized international birth date of 1st January 1952. The first product registration for Oradexon (N.V. Organon) was obtained in Hungary on January 1, 1959.

Clinical studies on the efficacy and safety of dexamethasone have already been published for several decades. Thus, the benefits and risks or the adverse reactions associated with the therapeutic use of dexamethasone in humans are well-known. Oradexon (N.V. Organon) contains dexamethasone as the active ingredient. Dexamethasone is a synthetic derivative of the natural adrenal hormone cortisol.

The following formulations are available:

- Solution of 5.25 mg/ml or 5 mg/ml dexamethasone sodium phosphate, for systemic or intra-articular injection. Also available are 8mg/2ml, 4mg/ml Solution for Injection.
- Tablets containing 0.5, 1.5 or 2.0 mg dexamethasone per tablet, for oral use.

Dexamethasone (tablets) and dexamethasone sodium phosphate (injection) are fully compliant with the specifications of the European Pharmacopoeia Monographs 388 and 549, respectively, as described in the chemical/pharmaceutical documentation on Oradexon (N.V. Organon).

Oradexon (N.V. Organon) is used for the treatment of various inflammatory and autoimmune diseases.

IV.2 Non-clinical aspects

1. Introduction

Reference is made to the non-clinical aspects as reported in the Netherlands MEB Report on Dexamethasone: “The risks of administration of high dose dexamethasone to premature neonates” dated 21.12.2008 and to the relevant references to the literature quoted in that report.

2. Discussion on non clinical aspects

In animal studies, cleft palate was observed in rats, mice, hamsters, rabbits, dogs and primates; not in horses and sheep. In some cases these divergences were combined with defects of the central nervous system and of the heart. In primates, effects in the brain were seen after
exposure. Moreover, intra-uterine growth can be delayed. All these effects were seen at high dosages.

The above described effects are all observed after exposure in utero. The effects in primates have been observed after early third trimester exposure to dexamethasone by Uno et al. (1). They described dose-dependent alterations of brain structure and histology among the offspring of rhesus monkeys in doses at or above those used clinically.

From the animal studies, though mostly from one group, there are indeed indications that there is a risk for long term effects on brain (learning capability, social response) and heart (reduced ventricular weight, dysfunction). These effects in animals should be mentioned in section 5.3 of the SmPC.

Whether these findings overrule the positive short term effects (originally outweighing the possible acute adverse effects of dexamethasone), resulting in a negative benefit-risk, is a clinical issue.

IV.3 Clinical aspects

1. Introduction

As in adults corticosteroids including dexamethasone have been used beneficially in children for a wide variety of diseases and conditions which occur in both populations. However, in the paediatric population there are some conditions such as their possible association with long term neuro-developmental negative effects when used in the first week of life in preterm babies and also their possible effects on growth and development when used in childhood which are peculiar to children. For these reasons the use of corticosteroids in infants and children merits special consideration.

2. Discussion on clinical aspects and conclusion

Overview of clinical pharmacology

Pharmacodynamics

In humans, cortisol is the main glucocorticoid. Glucocorticoids are produced and secreted by the adrenal cortex and are an intrinsic part of the hypothalamo pituitary adrenal-axis (HPA-axis). Fluctuations in the rates of secretion of glucocorticoids are determined by fluctuations in the release of ACTH by the pituitary corticotropes.

These corticotropes, in turn, are regulated by corticotrophin releasing hormone (CRH), a peptide released by corticotropin releasing hormone (CRH) neurons in the hypothalamus. There are three levels of regulation for the HPA-axis: diurnal rhythm in basal steroid production, negative feedback regulation by adrenal corticosteroids, and marked increases in steroid production in response to stress (2). Most effects of glucocorticoids are not immediate, but become apparent
after several hours. This fact is of clinical significance, because a delay generally is seen before beneficial effects of glucocorticoid therapy are observed (2).

Glucocorticoids, both naturally occurring (cortisol) or synthetic (e.g. hydrocortisone, prednisone, triamcinolone, dexamethasone), exert a broad range of effects on multiple organ systems and tissues, which will be briefly discussed below.

Physiological effects of glucocorticoids

In physiological concentrations glucocorticoids affect carbohydrate, protein and lipid metabolism (2) (3). Glucocorticoids stimulate hepatic gluconeogenesis, proteolysis and the generation of gluconeogenic precursors. Fatty acid mobilization and hepatic cholesterol synthesis are also enhanced by glucocorticoids. These effects of glucocorticoids can be viewed as critical survival responses to starvation and severe stress.

Other physiological effects of glucocorticoids

In physiological concentrations glucocorticoids have effects on fluid and electrolyte balance and exert multiple effects on calcium metabolism. Glucocorticoids are also important for the preservation of normal function of the cardiovascular system, the immune system, the kidney, the skeletal muscle, the endocrine system and the nervous system. In supraphysiological (pharmacological) doses exogenous glucocorticoids can suppress the HPA-axis via a negative feedback mechanism; they inhibit pituitary ACTH secretion, thereby reducing the production of glucocorticoids in the adrenal cortex (2), (3).

Anti-inflammatory and immunosuppressive actions of glucocorticoids

In pharmacological doses glucocorticoids are used to treat a variety of non-endocrine diseases, because of their anti-inflammatory and immunosuppressive effects.

Anti-inflammatory actions

Glucocorticoids can prevent or suppress inflammation in response to multiple inciting events, including radiation, mechanical, chemical, infectious, and immunological stimuli. By inhibiting the inflammatory processes at the cellular level, glucocorticoids decrease the clinical manifestations (e.g. heat, redness, swelling and pain), but the underlying disorder is unaffected. Glucocorticoids inhibit the production (by multiple cells (e.g. macrophages, monocytes, endothelial cells, basophils, fibroblasts and lymphocytes) of factors that are critical in generating the inflammatory response and in this way glucocorticoids can prevent a cascade of reactions.

Immunosuppressant actions

Mechanisms of immunosuppressant action are not completely understood but may involve prevention or suppression of cell-mediated (delayed hypersensitivity) immune reactions as well as more specific actions affecting the immune response. For instance, glucocorticoids suppress the immune response by inhibiting cytokine synthesis and action (2), (4). Thus, glucocorticoids are of immense value in treating diseases that result from undesirable immune reactions. These diseases range from conditions that predominantly result from humoral immunity (e.g. urticaria), to those that are mediated by cellular immune mechanisms (e.g. transplantation rejection).
Pharmacological actions of dexamethasone

Dexamethasone is one of the most potent synthetic analogues of the naturally occurring glucocorticoid, hydrocortisone. It has 6-7 times the anti-inflammatory potency of prednisolone and 25 times that of hydrocortisone (5). Dexamethasone has practically no water- and salt-retaining properties, and is therefore suitable for use in patients with cardiac failure or hypertension.

Pharmacokinetics

Absorption
Dexamethasone is rapidly and well (around 80%) absorbed when given by mouth. Peak plasma levels are reached between 1 and 2 hours after ingestion of dexamethasone tablets. After intramuscular (IM) and intravenous (IV) administration of water soluble dexamethasone sodium phosphate the onset of action is relatively fast (6).

Distribution
In general, glucocorticoids are readily absorbed from the gastro-intestinal tract. They are also well-absorbed from sites of local application. They are rapidly distributed to all body tissues. They cross the placenta and are excreted in small amounts in breast milk (6). Dexamethasone is reversibly bound (up to 77%) to plasma proteins, mainly albumin. Only the fraction of the corticosteroid that is unbound can enter cells to mediate corticosteroid effects (2).

Metabolism
After intravenous injection dexamethasone sodium phosphate is rapidly hydrolyzed to free dexamethasone, reaching its peak plasma concentration within 5 minutes. Dexamethasone metabolism in the liver is slow and rather limited. Studies suggest that the major metabolic pathway involves the formation of un-conjugated polar metabolites.

Excretion
The plasma half-life of dexamethasone is 3 – 4.5 hours, but as the effects significantly outlast plasma concentrations of steroids, the plasma-half life is of little relevance and the use of the biological half-life is more applicable. The biological half-life of dexamethasone is 36-54 hours (6).

In patients with liver disease dexamethasone clearance was reduced, due to an impairment of metabolism. In renal failure, on the other hand, clearance was increased due to acceleration of metabolism (7). The major route of excretion of dexamethasone and its metabolites is via the kidneys. After oral administration a large proportion (ca. 30%) of the total dose administered is likely to be excreted in the urine as unchanged dexamethasone.

After intravenous administration of dexamethasone phosphate, about 9% of the administered dose appeared in 24 hours in the urine as free dexamethasone.
3. Clinical overview

Review of the data provided regarding the use of dexamethasone treatment in the conditions mentioned below in adults and children confirms its efficacy and overall safety when used appropriately. They are serious, acute and chronic inflammatory and auto-immune conditions for which no adequate treatment had been available before the advent of corticosteroids.

There is a wide range of serious conditions occurring in adults and children reported in the medical literature which respond to dexamethasone treatment. These include:

1. Acute exacerbation of asthma and other pulmonary conditions
2. Anaphylactic shock
3. Initial treatment of autoimmune diseases
4. Cerebral oedema
5. Prevention and treatment of chemotherapy induced emesis
6. Prevention and treatment of post operative vomiting
7. Palliative treatment of malignant tumours
8. Treatment, initial, of acute severe/extensive skin diseases
9. Adrenal hyperplasia
10. Severe infectious diseases with toxic conditions
11. Treatment of active phase of progressive rheumatoid arthritis (RA)
12. Treatment of polytraumatic shock
13. Sub-conjuctival administration
14. Intra-articular injections, infiltration therapy

A single course of prenatal corticosteroid (CTS) therapy has been shown to accelerate foetal lung maturation when premature delivery is imminent with a reduction in morbidity in premature newborns by reducing the incidence of respiratory disease and dependence on mechanical respiratory support (8). Long term follow up has revealed no adverse effects at risk of premature delivery between 24 and 33 weeks of gestation.

CTS including dexamethasone have been widely used postnataally in preterms for the prevention of chronic lung disease. Early trials with dexamethasone in preterm infants have shown short term improvement in pulmonary function and shortened time on the ventilator. A range of
significant short-term adverse reactions regardless of onset of treatment was observed, including growth retardation, hypertension, infection, gastrointestinal bleeding, intestinal perforation and hypertrophic cardiomyopathy. All these short term adverse reactions are currently included in section 4.8 of the SmPC.

Regarding possible long-term effects there are emerging data in the literature that although there may be short term benefit early use may be associated with serious long term adverse effects. This was suggested by the studies of Yeh et al. (9) (10) (11) and by the studies of Shinwell et al. (12). Caution needs to be applied whilst interpreting these results as only few studies were sufficiently powered to detect any differences in long-term effects and almost all studies evaluating long-term effects of glucocorticoid treatment had methodological quality issues (13).

Because of the possible risks associated with early use (initiated before 96 hours after birth) in preterm neonates, dexamethasone should not be used routinely in the treatment of chronic lung disease in neonates. An assessment of the risk/benefit should be made on an individual patient basis depending on the particular situation and its severity.

For most of the authorised indications which may arise in children, data on dosage efficacy and safety are available. Dosage varies according to the severity of the condition being treated, the state of the patient and response to treatment.
V. MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION

Overall conclusion

Benefits and Risks Conclusion

Dexamethasone has a record of long established use of over 50 years. It has been shown to be effective in a wide range of indications as shown by several publications. The indications for which dexamethasone is used are severe and or serious diseases which are sometimes life threatening or which have the possibility of severe temporary or residual disability. If used appropriately alone or with other therapy e.g. with antibiotics in certain situations and with the optimum mode of administration the benefit/risk ratio is largely positive. Special care is needed in children.

The contraindications, warnings and precautions, and the adverse reactions profile of dexamethasone in the indications are well established and generally known.

However, dexamethasone in particular is a very powerful agent and caution is needed when it is used. In general steroids should only be used if no alternative treatment is available. If used in children special care needs to be taken because of the problems of development and growth and also because of the greater possibility of inducing suppression of the HPA-axis.

The overall benefit/risk ratio of dexamethasone continues to be beneficial. However, in view of the pre-clinical information following its use in animals and the clinical information about possible neuro-developmental adverse long term effects associated with its use when used in the first week of life in preterm babies the Summary of Product Characteristics (SmPC) and the Patient Leaflet (PL) should be updated so that the product will be used appropriately. For these reasons it has been proposed that the SmPC and the PL should be updated by information as per Recommendations (Section II and below).

Recommendations

The recommendations for changes/additions to the SmPC and PL are as follows:

1. SmPC

Section 4.4 Special warnings and precautions for use:
Preterm neonates: “Available evidence suggests long-term neurodevelopmental adverse events after early treatment (< 96 hours) of premature infants with chronic lung disease at starting doses of 0.25mg/hg twice daily.”

Section 4.6 Pregnancy and lactation:
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2. PL

The following information should be added under “Pay attention when using Dexamethasone”:

“Dexamethasone should not be used routinely in preterm neonates with respiratory problems.”

A Type IB variation to be requested from the MAH within 90 days of the publication of this Public Assessment Report (PAR).
VI. LIST OF MEDICINAL PRODUCTS AND MARKETING AUTHORISATION HOLDERS INVOLVED

1.) List of medicinal products

- Oradexon
- Aacidexam
- Dexamethasone
- Fortecortin

Strength:
- 0,5mg, 1,5mg and 2mg tablets and
- 5mg/ml, 8mg/2ml, 4mg/ml Solution for Injection

2.) Marketing Authorisation Holders:

-N.V. Organon, The Netherlands
-Organon Laboratories Limited, U.K
-Organon Portuguesa, Lda., Portugal

-Merck & Co., Inc

Comment:
At present N.V. Organon is an indirectly owned subsidiary of Merck & Co., Inc.
Schering-Plough Central East AG located at Weyenstrasse 20, 6000 Lucerne 6, Switzerland, is an indirectly owned subsidiary of Merck & Co., Inc.

The companies mentioned above, including their affiliates, are trading and operating under the trade name MSD outside the United States and Canada

Also refer to: Line listing (13th wave List with studies) from EMA
VII. REFERENCES


(8) NIH CDP, 1995; Roberts and Dal


